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# Policy Issues in Pharmacogenetics



**Policy Briefing from the  
UK Pharmacogenetics Study Group  
July 2006**

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## The UK Pharmacogenetics Study Group

The UK Pharmacogenetics Study Group is a group of social scientists from several UK universities actively engaged in examining issues around the development and clinical introduction of pharmacogenetics—the relationship between individuals' genetic profile and drug response—into health care systems.

This policy briefing is the result of several years cumulative research by the authors on the social, ethical and economic aspects of pharmacogenetics funded by The Wellcome Trust, whose support is gratefully acknowledged. Additional support for individual authors from the Economic and Social Research Council, the Medical Research Council, the Department of Health, and the European Commission is also acknowledged.

Pharmacogenetics promises to improve health care in a number of ways. However, as this policy briefing highlights, many questions remain to be answered before the promised benefits are realised in routine clinical practice. The most basic of these include the scale and applicability of the technology and the timeframe for adoption, and the need for robust evidence of cost-effectiveness and clinical utility. At the same time, it is increasingly recognised that research from a social science perspective offers important insights into the development and, equally as significant, introduction of new health technologies. Research on pharmacogenetics has been particularly well supported in the UK by bodies such as the Wellcome Trust, with results from a number of empirical studies now published in the academic literature. However, dissemination to the wider health care policy community, including politicians, regulators, senior managers and other decision makers, has been less visible and widespread. Our aim in publishing Policy Issues in Pharmacogenetics is to help rectify this state of affairs by providing a succinct analysis of the main issues that need to be resolved before the potential benefits of this important technology can be realised, based upon this research.

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# Policy Issues in Pharmacogenetics

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## Contents

|  |           |
|--|-----------|
| <b>Background</b>                      | <b>2</b>  |
| <b>Scientific Background</b>           | <b>2</b>  |
| <b>Industry and Pharmacogenetics</b>   | <b>3</b>  |
| <b>Clinical Trials</b>                 | <b>5</b>  |
| <b>Clinical Adoption</b>               | <b>6</b>  |
| <b>Regulators and Pharmacogenetics</b> | <b>8</b>  |
| <b>References</b>                      | <b>11</b> |
| <b>About the Authors</b>               | <b>13</b> |

## Key findings

- This report is directed at UK-based policymakers with the aim of informing policies to protect and promote public health.
- Current pharmaceutical industry strategies mean there is a risk that one form of pharmacogenetics (pre-prescription genotyping for already licensed drugs) that may have considerable public health benefits will not enter common use.
- Diversity of regulations concerning DNA sampling across the EU is hampering the kinds of international research required to develop robust pharmacogenetic data.
- Diffusion of pharmacogenetics into clinical practice requires building public and professional confidence around the technology (for example, by taking ethical concerns seriously), and improving the evidence base for policy decisions.
- Current EU rules mean that pharmacogenetic tests are regulated in a confusing and possibly dangerous way since manufacturers self-certify such tests and do not have to provide data on their accuracy.

## Background

In recent years, a number of organisations have debated the regulatory and policy issues arising from pharmacogenetics/pharmacogenomics. These organisations include regulators of medicinal products such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and other bodies such as the Nuffield Council on Bioethics and the Royal Society. This report contributes to these debates by presenting empirical research funded by the Wellcome Trust<sup>1</sup> on the social, ethical and economic aspects of pharmacogenetics, with the aim of informing policies to protect and promote public health. This report is not comprehensive and does not claim to cover all possible issues raised by pharmacogenetics; rather, it focuses on those areas where recent research has generated empirical evidence.

The intended audience for this report is UK-based policymakers, including people from the Medicines and Healthcare products Regulatory Agency (MHRA), Department of Health, Human Genetics Commission, and parliamentarians (such as members of Health or Science and Technology Select Committees). We hope that it will also be of value to international policymakers (such as the EMA, Organisation for Economic Cooperation and Development, and the European Commission) and those in industry, academic researchers and clinicians.

Discussing policy issues around an emerging technology such as pharmacogenetics comes with the risk that one will be seen as automatically assuming the technology will come into widespread use. We recognise this but note that suggesting that there may be a public health benefit from the development of pharmacogenetics does not mean we uncritically accept that this technology will develop as its supporters claim it will. The introduction of pharmacogenetics may reduce the incidence of adverse drug reactions or

improve the efficacy of treatments, but it is worth noting that there are a number of simpler interventions that might have the same effect.<sup>2,3</sup> The aim of this briefing is to provide policy makers with evidence that may help deal with the issues raised by the current and anticipated development of pharmacogenetics.

## Scientific Background

**Definition** Inherited variations can influence the way drugs affect humans, as has been noted since the time of the Ancient Greeks. However, it was only in the 1950s that the study of such variations gained a title – pharmacogenetics – and only in the late 1990s, as the Human Genome Project moved into high gear, that industry became interested and its widespread use was seriously debated. The research literature abounds with examples of the way in which genetic variation influences drug responses, covering a wide range of drugs, diseases and interactions. Some of the most important and well-known examples are summarised in the Boxes below.

**Applications** There are two main potential applications of pharmacogenetics. The first is to improve drug prescribing by introducing genetic testing before prescription. For example, different versions of the gene CYP2D6 can lead to variations in the rate at which someone metabolises drugs for a range of common conditions, including heart disease, high blood pressure, and some psychiatric conditions. ‘Fast metabolisers’ may process a drug so quickly that a normal dose has no therapeutic effect, while ‘slow metabolisers’ require much-reduced doses to avoid the risk of an adverse reaction. Therefore having information about a patient’s ability to metabolise a given drug can improve the effectiveness of therapy or avoid the risk of serious side effects. A good example of this is TPMT testing for thiopurine drugs (see Box 1 overleaf).

The second main way in which pharmacogenetic data and testing can be applied is during the

process of drug development. Large pharmaceutical companies are now using the technology routinely to ensure that new medicines are either safe and effective in the whole population, or are targeted to specific, genetically-defined groups of 'good responders'.

**Potential benefits** Supporters of pharmacogenetics suggest that it will bring about a number of clinical, commercial and public health benefits. These include improved patient care through reduced adverse drug reactions and the targeting of drugs to good responders as well as reduced prescription costs since drugs would not be given to patients who will not benefit from them. In the case of industry, the hope is that pharmacogenetics will allow the early identification of drugs that are going to proceed to market, avoiding the situation where considerable sums are spent developing drugs, only for them to fail at the late stages of clinical trials. This would reduce the amount of money that goes into developing products that fail at the final hurdle, hopefully reducing the costs of drug development. It remains to be seen whether these benefits will be realised in practice, but the promise of the technology has prompted much public and private investment in the field.

## Industry and Pharmacogenetics

While regulators, policy makers and users will be involved in the development of pharmacogenetics, the evolution of the technology will be driven by investment from industry, largely because of the high costs of drug development including clinical trials. Most of the world's leading pharmaceutical companies, together with nearly 50 smaller biotechnology and genomics firms (mainly working on diagnostic tests), are investing in pharmacogenetics.<sup>4</sup>

**Strategies** Broadly speaking three main technology and business strategies are being adopted by industry, each of which can be used to im-

### Box 1: Thiopurine drugs & TPMT

Drugs from this family, such as azathioprine and 6-mercaptopurine act as immunosuppressants and have been used for decades to treat autoimmune conditions and leukemia. These drugs have significant toxicity, especially for those patients with inherited deficiency in the enzyme thiopurine methyltransferase (TPMT), who are prone to bone marrow damage when given the drugs. The expectation is that genetic screening could be used to identify the 1 in 300 people with this deficiency who would need a lower than normal dose of the drug. Genetic screening could also be used to identify fast metabolisers who may benefit from increased doses.

prove drug safety or enhance the efficacy of treatment.

- **Improving the process of drug discovery and development** Large companies are mainly focusing on the application of pharmacogenetics in their internal drug development programmes. In particular, they are using pharmacogenetic techniques to strengthen pre-clinical safety testing and to improve the design of early stage clinical trials. For example, as many drugs are metabolised by the Cytochrome P450 enzymes and genetic variation in these enzymes is a major source of adverse drug reactions, companies are using pharmacogenetic technology to ensure that new drugs will not be affected by these genetic variations.<sup>4</sup>
- **New targeted therapies** Large companies are also starting to launch new medicines that are targeted at patients with particular genotypes. For example the breast cancer drug trastuzumab (Herceptin, Roche/Genentech) is only effective in the 30% of women who are positive for the HER2 marker (Box 2). Where a drug is licensed for a particular group, it will have to be used with a companion diagnostic test (a so called drug-test combination). At present, relatively few therapies of this sort are reaching the

market; typical examples are the anti-cancer agents trastuzumab (Herceptin, Roche/Genentech), imatinib (Glivec, Novartis) and cetuximab (Erbix, Merck KGaA/ImClone/Bristol-Myers Squibb).<sup>4, 5</sup>

### Box 2: Trastuzumab & Her2

Trastuzumab (marketed as Herceptin) was licensed for use in the UK in 2000 and is used to treat end-stage breast cancer in those women whose tumours produce too much of a protein called HER2. Prior to treatment tumour tissue is tested to assess its HER2 status, and around 30% of patients are eligible for treatment. Trastuzumab was the first drug to be approved for use in association with a diagnostic test by regulators, and hence may be thought of as the first intentionally 'pharmacogenetic drug'. Regulatory approval for the treatment of early stage HER2-positive breast cancer was given in May 2006.

- Applying pharmacogenetics to already licensed medicines** Smaller firms are focusing on the development of new diagnostic tests, mainly for drugs that have already been licensed. Genotyping patients before treatment could help avoid the prescription of a particular drug to patients at risk of adverse drug reactions or to those who would not respond to therapy. One of the best examples of this approach is the test for TPMT (see Box 1). However, despite the obvious public health value of such tests, there is still uncertainty over industry's long-term interest in this approach. Most commercial interest in pharmacogenetics centres on its use in research: for example, as of September 2005 most pharmacogenetic tests in development or on the market were tests for CYP450 genes (see Box 3) for use in clinical trials and were thus aimed at research rather than clinical use. Interest in clinical applications has increased recently, and in the past six months tests *have* begun to enter the market

(such as for warfarin, and UGT1A1/irinotecan from the US company Third Wave Technologies). But very few pharmacogenetic tests have been submitted for clearance by regulatory authorities and there are thus only a limited number of such tests available for clinical use. Furthermore, at present there is limited evidence of clinical demand for this application.<sup>4</sup>

Each of the above options is at a different stage of development and each has varying levels of investment. Particular applications will only be successful if they command sufficient clinical and commercial support. Although there are some examples on the market, great commercial uncertainty still surrounds the second option listed above (i.e. the creation of new medicines targeted at stratified patient populations). It is not clear whether companies will find smaller potential markets sufficiently attractive to justify investment in this application of pharmacogenetics.

In addition, at present it appears that large pharmaceutical companies are not very interested in the development of pharmacogenetic testing for already licensed drugs, a potential area of significant public health benefit, as there is little commercial incentive. As a consequence, the small firms working in this area may not have the resources required to get pharmacogenetic testing for already licensed drugs to market as they would normally seek to do this in partnership with larger companies.<sup>4</sup>

Even if they were to be successful, this might conflict with the economic interests of companies producing licensed drugs while they are still under patent. There is some evidence that large pharmaceutical companies are willing to intervene in clinical trials aiming to develop such tests. For example, in the case of Alzheimer's drugs already on the market, large companies have prevented the publication of trial data supporting the genetic stratification of the patient population, as well as attempting to derail an independent trial of one such drug that included a



pharmacogenetic component, by refusing to supply the relevant drug (and placebo).<sup>6</sup> While this is only one example, it is a behaviour that has been predicted for some time<sup>7</sup>, and which is in keeping with previous industry activities<sup>8</sup> and current political concern about the pharmaceutical industry.<sup>9</sup>

It is important to note that although industry may play the major role in the development of pharmacogenetics, given funding, the non-commercial sector can also develop pharmacogenetic tests. A good example of this is the MODY (maturity onset diabetes of the young) gene programme. This tests 'Type 1' diabetics and identifies those people with the HNF-1alpha and KIR6.2 mutations who respond poorly to insulin, and allows them to be put on sulphonylurea drugs. In clinical trials this group of patients have been shown to do extraordinarily well on these drugs. There are considerable numbers of 'Type 1' diabetics in the UK with the relevant mutations, and a national network of diabetes nurses are being trained in this approach.<sup>10</sup>

**Conclusions** There is a real chance that the potential public health benefits offered by pre-prescription genotyping of already licensed drugs will not be realised due to 'market failure'.<sup>11</sup> While the commercial development of such tests remains the responsibility of companies, mechanisms already exist for governments to intervene in the commercial research and development process to encourage research in particular directions. For example Orphan Drugs legislation offers tax and regulatory benefits to companies that develop drugs for rare conditions. In addition to such 'indirect' approaches to stimulate industrial investment, more public investment in clinical studies to help develop the evidence base could be adopted to support this option for the technology (as has already happened in the UK in the case of warfarin). All of these options could also be developed at the EU level.<sup>12, 13</sup>

## Clinical Trials

As has already been noted, the most widespread use of pharmacogenetics in current clinical trials is for internal purposes, to exclude those drugs where there is a wide variation in response according to common genotypes (usually the CYP450s as described above). But many current clinical trials do involve the sampling of DNA, which is then stored for unspecified future pharmacogenetic purposes. Such trials have taken place since the late 1990s,<sup>14</sup> and as a consequence a number of large multinational pharmaceutical companies are building extensive genetic databases.<sup>15</sup> The exact size and number of such industry DNA collections is not known since there is no requirement upon companies to declare them. It is notable that while there has been considerable public and policy debate over the development of public or partly public DNA databases such as UK Biobank, with concerns often being raised about commercial access, there has been little or no public discussion over the commercial development of similar DNA banks through the collection and long term storage of samples in pharmacogenetic clinical trials.<sup>16</sup>

An international committee set up by pharmaceutical companies to debate policy in this area, has tried to introduce a degree of standardisation around industry practice involving such DNA sampling.<sup>17</sup> However, while the Clinical Trials Directive governs all clinical trials in the EU<sup>18</sup> these regulations do not specifically deal with pharmacogenetics, and there is considerable variation across the EU in regulations relating to DNA sampling. For example, the UK has no regulations specifically governing the sampling of DNA in clinical trials, although there are a number of regulations that touch on this such as the Human Tissue Act 2004 or the Data Protection Act 1998. In Sweden, by contrast, the Ethical Review Act of 2003 requires investigators to seek permission for secondary (i.e. not previously specified) research

on stored DNA samples from a Research Ethics Committee. This Committee may decide that the new research has to be advertised and participants whose samples are in storage given the option to opt out.<sup>19</sup>

One consequence of this variation is that firms working in a number of EU member states suggest that Europe is becoming an increasingly difficult research environment for studies sampling DNA for storage. In part this is due to individual countries, such as Sweden or France, with restrictions over this sort of research. But more than this, firms find that abiding by multiple frameworks in this area is a logistical challenge. The big differences in the detail of provisions between countries, and the fact that they are continually changing makes it difficult for firms to comply with the resulting procedural changes.<sup>20</sup> Furthermore, this variation means that researchers working on multinational projects may be acting unlawfully if they share data and samples across borders.<sup>21</sup> It may thus become a barrier to international studies that attempt to combine data to achieve the greater statistical power needed to provide robust pharmacogenetic tests that work on broad populations.

**Conclusions** A strong case can be made for harmonisation of the ethical frameworks for pharmacogenetic trials (beyond the harmonisation that has already been achieved through the Clinical Trials Directive).<sup>12,13</sup> The question then remains whether such harmonised legislation should standardise 'downwards' - requiring member states with specific regulations to lower them to a common level - or whether those member states with no specific regulations should raise the protection offered on DNA samples.

## Clinical Adoption

For many commentators, the largest hurdle for pharmacogenetics will be the transition from the laboratory into clinical practice. The issues involved are complex and include considerations of the ade-

quacy of the scientific evidence, cost, differences in the knowledge base, and ethical concerns.

**Adequacy of scientific evidence** While some pharmacogenetic tests may provide unequivocal information on the best drug, preferred dose, or likelihood of adverse events, most tests will provide only broad probabilities.<sup>22</sup> Several commentators have pointed to the need for a more robust evidence base, since clinical outcomes are dependent on many other variables besides genetics (such as age, gender, lifestyle, other drugs consumed, patient compliance etc). To enable introduction, it will be necessary to demonstrate on a case by case basis the likely benefits and costs involved, in terms of both patient benefit and cost effectiveness.<sup>11,13</sup> Limited evaluation will provide scope for creative marketing, variation in clinical uptake and costs and uncertainty about true benefits and risks.<sup>23</sup> As discussed in the next section, this is particularly relevant in the EU where the manufacturers of pharmacogenetic (and other biomedical) tests do not have to prove that their tests are useful in a clinical setting (i.e. their clinical validity) in order to market them.

In addition, for statistical reasons the incidence of rare but often serious adverse reactions cannot be determined before approval and marketing. In general, robust post-marketing surveillance, termed 'pharmacovigilance' by the EU, is required to determine the true extent of adverse drug reactions and their cause, and the collection of pharmacogenetic data on new products, including tests, would provide valuable safety information. This is particularly likely in the case of so-called idiosyncratic reactions, such as unexpected cardiac arrhythmias leading to sudden death, which are often independent of dose. These are unlikely to emerge during drug development or clinical trials for marketing authorisation purposes, and the use of pharmacogenetics in post-marketing surveillance could help uncover the factors responsible. However, there has been little regulatory action in this area to date. Off-label use, prescribing



a drug outside the approved indications - for example on children, is also common and pharmacogenetics complicates the issue further. This is because it may lead to a situation where rather than doctors prescribing off-label because of a lack of data about the drug's effectiveness in a particular group (as is currently the case) drugs may be prescribed even though it is known that they are unlikely to work in a particular person, because of their genes. This relates to other new issues in this area such as the rights of patients to medicines, even if they refuse to give consent for a genetic test.<sup>13, 24, 25</sup>

**Cost considerations** The lack of a well-developed evidence base in relation to cost-effectiveness is a significant reason for non-uptake of pharmacogenetics. It is important to note that in the few cases where a pharmacogenetic treatment has been assessed for clinical and cost effectiveness by the National Institute for Health and Clinical Excellence (NICE), the pharmacogenetic nature of the drug concerned was largely irrelevant to NICE's decision; far more important were its cost and how effective it was (for example, trastuzumab in 2002).<sup>6, 26</sup> Even where cost benefits are apparent to the health-care system as a whole, costs and benefits may accrue to different departments within the same hospital, meaning that diffusion needs to be supported with policy-guidelines and additional funding. For example, due to the cost of the test, some doctors have been resistant to the idea of testing hundreds of patients to identify those few with mutations in the TPMT gene who may suffer an adverse reaction when treated with thiopurine drugs (Box 1). However, they may be unaware of the costs of an adverse reaction borne by other departments in the hospital.<sup>27</sup>

**Knowledge differences** A common view among policy debates is that clinicians' knowledge and education levels are the deciding factor in the uptake of this technology.<sup>28, 29</sup> These debates tend to focus on General Practitioners, yet

### Box 3: Warfarin & CYP450 enzymes

Warfarin is widely used to thin the blood in conditions such as deep vein thrombosis and atrial fibrillation and to prevent clots forming in people susceptible to strokes. Variations in the gene CYP2C9 affect patients' ability to metabolise warfarin. People with particular mutations run three times the normal risk of developing serious bleeding problems when they take the drug. The Department of Health is currently funding a prospective study to identify the genetic and environmental factors that determine warfarin dose requirements with a view to developing an algorithm that predicts individual doses.

although pharmacogenetics *may* enter general practice in the future (a good example might be warfarin, Box 3) at present pharmacogenetics is more relevant in secondary/tertiary care. Examples of this technology are already in use in oncology: trastuzumab (Herceptin, Roche/Genentech) used to treat breast cancer (Box 2), and imatinib (Gleevec, Novartis) used to treat a form of leukaemia called chronic myeloid leukaemia.

While knowledge deficits may underpin slow diffusion of pharmacogenetics in some instances<sup>20</sup> and education about pharmacogenetics will be important, it is also true that research suggests that the specialist knowledge of secondary-care clinicians means that they sometimes have more up-to-date views (and more practical understandings) of the clinical application and usefulness of specific tests than many academic and industry supporters of pharmacogenetics. For example, the link between the APOE4 gene and response to the Alzheimer's treatment tacrine (Cognex, Parke-Davis), which policy makers and supporters of pharmacogenetics have presented as a good example of pharmacogenetics, is viewed sceptically by disease specialists and experts in Alzheimer's genetics.<sup>6</sup>

**Ethics** Although some supporters claim that pharmacogenetics has nothing to do with 'traditional' disease genetics<sup>30</sup>, it is clear that some pharmacogenetic tests provide information on disease susceptibility and prognosis, a point accepted by leading industry supporters of pharmacogenetics,<sup>31, 32</sup> and that clinicians are aware of and are concerned about how to manage such overlaps. Thus pharmacogenetics cannot be wholly separated from broader ethical concerns about other forms of genetic testing such as the relevance of test results to patients' families.<sup>6, 33</sup>

Preliminary research exploring the public's attitude to pharmacogenetics supports the need to engage with these ethical issues. A number of studies suggest that the public is generally supportive of medical genetic testing as a whole,<sup>34</sup> and that there is broad public support for pharmacogenetics both in terms of research<sup>35</sup> and clinical use.<sup>36</sup> At the same time there are genuine ethical concerns about third-party access to genetic data,<sup>37</sup> the possible costs of pharmacogenetic drugs, and the potential for discrimination problems involving pharmacogenetic reactions mapping onto ethnicity ('racial medicine'),<sup>37, 38</sup> although these seem to be more of a concern in the US than the UK.<sup>13</sup> This last point is particularly pertinent in light of the FDA's decision in June 2005 to license a drug called BiDil for the treatment of cardiovascular disease in African-Americans. While overall the drug was shown to have increased effectiveness in African-Americans (who also do not respond as well to conventional treatment), this will not be true for every individual since response to the drug may depend on both social and biological differences, which do not map directly onto race. Thus concern has arisen that there is a risk that race or ethnicity will become a 'shorthand' for pharmacogenetic status, even though the underlying genetic basis for any differential response has not been demonstrated. This might have a potential discriminatory effect, for example leading to prescribing on

the basis of ethnicity rather than individual need.<sup>39, 40, 41</sup>

**Conclusions** Moving pharmacogenetics into the clinic will be challenging. Building public and professional confidence around the technology will be essential, as will improving the evidence base for policy decisions. Deliberately seeking the views of clinical users of this technology at all levels (e.g. nurses, pharmacists, laboratory staff, doctors) would broaden the range of views contributing to policy discussion, give access to the most up-to-date technical opinions, and highlight potential ethical problems. It would also encourage discussions with clinicians over the clinical and cost effectiveness of particular treatments.

## Regulators and Pharmacogenetics

As the organisations which decide whether a drug can be marketed or not, regulatory agencies are key players with regard to the adoption of pharmacogenetics-based treatments and the timeframe within which this occurs.<sup>42</sup>

**Current regulation** When considering the possible options open to drugs regulators in the UK and EU, a useful comparison can be made with the US, where the regulator, the Food and Drug Administration (FDA), is encouraging pharmacogenetics through a number of approaches. This has been done by including measures aimed at encouraging the approval of innovative medical therapies in the agency's 'Critical Path' initiative, hopefully making product development more predictable and less costly.<sup>43</sup> Specific pharmacogenetics measures adopted by the FDA include:

- Publication of guidance on how the agency will handle genetic data - a crucial first step to overcoming uncertainty and industry concerns about confidentiality and intellectual property<sup>44</sup>
- Developing a framework for drug-diagnostic co-development<sup>45</sup>
- Introducing the Voluntary Genomic Data Submission (VGDS) initiative to encourage companies to submit exploratory pharmacogenetic

data not required for formal submission purposes in order to foster mutual learning and technical knowledge.<sup>46</sup>

There are a few examples where the FDA has included testing information before the approval of a drug, which underline the important role that regulatory agencies could play in relation to pharmacogenetics' move into the clinic. The attention-deficit hyperactivity disorder drug atomoxetine (Strattera, Lilly) is an example where the FDA included pharmacogenetics data relating to adverse drug reactions at time of approval, an occurrence that is likely to increase over time as targeted treatment approaches are adopted. Trastuzumab (Herceptin, Roche/Genentech; Box 2) is an example where pharmacogenetic data relating to the drug's efficacy was included prior to approval, as well as mandating testing prior to the drug being prescribed.

The FDA has also adopted a policy of reviewing marketed drugs when relevant pharmacogenetic data with a bearing on treatment outcomes becomes available and has already re-visited a number of approved products. In general, it has opted to provide clinicians with information on the relationship between different genetic variants and probable outcomes (such as efficacy or adverse events) but has not recommended specific action. The onus is on the clinician to decide whether to perform a test (and to determine if a suitable test is in fact available). To some extent, the significance of such re-labelling depends upon the therapeutic index of the drug. This is the ratio of the toxic dose to the therapeutic (i.e. effective) dose, and is often used as a measure of the relative safety of the drug for a particular treatment. Pharmacogenetics is more likely to be clinically useful (and cost effective) where the therapeutic index is narrow (i.e. when there is a small difference between toxic and efficacious doses).

Examples of post-approval label changes include the anti-cancer agent irinotecan (Camptosar,

Pfizer), and the inclusion of pharmacogenetic data relating to TPMT testing prior to use of the anti-leukaemia drugs, 6-mercaptopurine and azathioprine (Box 1). FDA recommendations for the widely used anti-clotting agent, warfarin (Box 3) – viewed by many observers as the paradigmatic case for demonstrating clinical introduction – were reviewed in November 2005 and the label is expected to be revised to include pharmacogenetic data shortly.<sup>47</sup>

However, it is important to note that simply re-labelling will not guarantee a change in clinicians' behaviour. Uptake in a particular therapeutic area will relate to the specific context of use. For example, it will be difficult to deny treatment with a 'drug of last resort' (such as the anti-schizophrenia drug, clozapine) whatever a pharmacogenetic test says about its likely effectiveness in a particular individual. It seems unlikely that professional acceptance will be forthcoming where current practice is considered acceptable and where the use or practicability is unclear.<sup>11</sup>

In the EU, the European Medicines Agency (EMA) has focused on clarifying pharmacogenetic terminology<sup>48</sup> and has also introduced a system of Briefing Meetings that allow sponsors and regulators to discuss pharmacogenetic data informally at an early stage.<sup>49</sup> These take place under the auspices of the agency's Pharmacogenetics Working Group - a process roughly equivalent to the FDA's VGDS initiative. Publication of a formal EMA guideline document is expected shortly.

**Inconsistencies** In the UK, the biggest challenges presented by regulators to the development and uptake of pharmacogenetics are the internal inconsistencies within European regulation. The EU system currently locates responsibility for drug regulation mainly at the EU 'level' while responsibility for biomedical tests, including pharmacogenetic testing, resides with member states. There is, therefore the potential for regulatory delay, or even disagreement and conflict. The most likely situation will be as in the case of

trastuzumab, where the EMEA approved the drug but could not approve the Her2 test, as it has no jurisdiction over devices. This is in contrast with the US where the FDA was able to clear Herceptin as a co-developed drug-device. Alternatively, it is possible, though unlikely, that the EMEA could approve a pharmacogenetic drug while national regulators reject the test related to it. While the EMEA is careful to evaluate the performance of a test co-developed with a drug and have a range of diagnostic expertise to draw on in this regard, it has no legal authority over such tests. This situation is at best ambiguous.

More importantly the *in vitro* diagnostics directive<sup>49</sup> has introduced a degree of ambiguity over regulatory requirements for data on clinical validity, i.e. the relationship between the genotype and the phenotype (in this case, the actual way in which drugs are processed by and affect the body). In the case of a CYP450 mutation, for example, a claim of clinical validity would be that the gene plays a role in the metabolism of a range of drugs. At the most basic level, the standard of evidence for tests is generally thought to be lower than that for drugs, where clinical trials are used to demonstrate clinical validity prior to approval. In addition, many pharmacogenetic tests are likely to be 'home brews'<sup>20</sup> – diagnostic tests developed by clinical laboratories for 'in-house' use – with some such tests already in use. A major concern is that these tests are not regulated to the same extent as marketed diagnostics.<sup>11, 24, 25</sup>

However, this is largely irrelevant to tests in the EU. Although the directive did introduce common regulatory requirements for the safety, quality and performance of diagnostic tests, this has not been interpreted as a requirement to demonstrate clinical validity if the manufacturer makes no clinical claims. A test can be described as identifying a specific gene, yet there is no requirement for manufacturers to explain the clinical significance of this link: what disease the gene might be a risk factor for, or what drugs the

gene might contraindicate. While this may not be an issue for many biomedical tests, the link to prescribing makes a pharmacogenetic test potentially more risky, and the lack of clinical validity data for pharmacogenetic tests potentially more problematic.

In addition, in the European system pharmacogenetic tests, like all other genetic tests, are classified by default as low-risk, so manufacturers can place them on the market without any evaluation by the regulatory authorities. Self-certification dossiers, which contain manufacturers' evaluative data on their tests, are kept secret, with national regulators such as the MHRA only 'calling in' the documentation if they have concerns. Given recent worries over secrecy about clinical evidence for drugs<sup>9</sup> it seems unusual for EU regulations to allow secrecy over the clinical evidence for pharmacogenetic tests. And as noted above, it is not clear that pharmacogenetic tests should be classed as low-risk. If a test for a genetic disease is unclear then the consequences may well be less severe than a pharmacogenetic test where a serious adverse reaction may result or, equally as important in cases such as cancer treatment, where lack of efficacy is likely. There is a strong case for making the information contained in self-certification documents publicly available, so that both clinicians and patients can access validation and performance data for such tests, and can make a genuinely informed decision.

**Conclusions** Although regulatory agencies in the US and, to a lesser extent the EU, are driving the translation of pharmacogenetics into clinical practice, adoption is slow; interviews suggest that regulators themselves are increasingly pessimistic about the speed of uptake.<sup>42</sup> In addition to the clarification of issues surrounding drug labels which could also support the development of pharmacogenetics, one obvious solution would be to clarify the uncertainty surrounding the EU regulatory framework. This could resolve the anomalous situation regarding both the different



levels at which drugs and biomedical tests are assessed in Europe, and the lack of a need to demonstrate clinical validity in the case of clinical tests, including genetic tests. Given the potential of pharmacogenetics to improve the safety and efficacy of drugs, and its dependence on the use of tests whose predictive value has been well-evaluated and is clearly understood, such a move could be made on the grounds of a potentially pressing public health need.

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